This large multicentre study is a valuable contribution towards efforts to improve the diagnostic evaluation of suspected tuberculosis disease. The authors reported that second-generation IGRAs (incorporating the additional antigens Rv3615c or Rv3879c) had higher sensitivity than T-SPOT.*TB* assays. They concluded that in low-incidence settings these tests "might have sufficiently high sensitivity...to facilitate prompt rule-out of tuberculosis".

As highlighted by the authors, this study did not include children, and therefore this conclusion might not necessarily apply to this age group. Substantial differences exist between the immune response to *Mycobacterium tuberculosis* in children and adults, and results from studies in adults cannot simply be extrapolated to children. These differences could explain why a study evaluating novel IGRAs in children younger than 5 years in India reported that enhanced enzyme-linked immunospot assays, using Rv3615c-encoded and Rv3879c-encoded antigens, did not improve the diagnostic performance of the standard enzyme-linked immunospot assay (which makes use of ESAT-6 and CFP-10 antigens).[2]

Furthermore, the study used the QuantiFERON-TB (QFT) Gold in-Tube assay that has since been replaced by the QFT-Plus assay, which was developed to improve sensitivity for detecting active tuberculosis by differentially stimulating CD4 and CD8 T cells. However, a 2019 study in children in a high-tuberculosis burden setting found no difference in performance between these two assays,[3] and similar results have been reported in adults.[4]

Several promising new immunological biomarkers (other than interferon-γ) that might enable the development of improved tuberculosis immunodiagnostic tests for children, have been identified in the past few years.[5] These biomarkers include various mycobacteria-specific cytokine responses that have better performance characteristics than interferon-γ and might simultaneously facilitate the distinction between latent and active tuberculosis.[6] A test with the ability to make this distinction would be a major advance in facilitating clinical management. In addition, high rates of indeterminate (ie, uninterpretable) assay results in young children remain a major issue. As current IGRAs do not have sufficiently high sensitivity to exclude tuberculosis disease in children, and microbiological diagnosis in this age group is difficult, developing a reliable triage test remains a high priority. In the search for next-generation immunodiagnostic tests for tuberculosis that perform more robustly across all age groups, it is therefore vital that children are included in future early-phase studies.

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1 Whitworth HS, Badhan A, Boakye AA, et al. Clinical utility of existing and second-generation interferon-γ release assays for diagnostic evaluation of tuberculosis: an observational cohort study. *Lancet Infect Dis* 2019; **19:** 193–202.

2 Shaikh N, Gupte A, Dharmshale S, et al. Novel interferon-gamma assays for diagnosing tuberculosis in young children in India. *Int J Tuberc Lung Dis* 2017; **21:** 412–19.

3 Kay AW, DiNardo AR, Dlamini Q, et al. Evaluation of the QuantiFERON-Tuberculosis Gold Plus Assay in children with tuberculosis disease or following household exposure to tuberculosis. *Am J Trop Med Hyg* 2019; **100:** 540–43.

4 Petruccioli E, Vanini V, Chiacchio T, et al. Analytical evaluation of QuantiFERONPlus and QuantiFERON-Gold In-tube assays in subjects with or without tuberculosis. *Tuberculosis* 2017; **106:** 38–43.

5 Togun TO, MacLean E, Kampmann B, Pai M. Biomarkers for diagnosis of childhood tuberculosis: a systematic review. *PLoS One* 2018; **13:** e0204029.

6 Tebruegge M, Dutta B, Donath S, et al. Mycobacteria-specific cytokine responses detect tuberculosis infection and distinguish latent from active tuberculosis. *Am J Respir Crit Care Med* 2015; **192:** 485–99.

Linezolid for drug-susceptible tuberculosis

We appreciate the interest in and comments on our trial by Hüseyin Bilgin and colleagues[1] and Saiam Ahmed and colleagues,[2] which was done to assess the substitution of ethambutol with linezolid during the intensive phase of treatment of pulmonary tuberculosis.[3] Several concerns were raised regarding our analysis of the results.

The first concern was our exclusion of 27 participants from the modified intention-to-treat analysis. As illustrated in figure 1 of the Article,[3] 18 participants were excluded because they did not take the trial medication at all, and nine were excluded because of protocol violations, including absence of information regarding HIV antibody concentration or urine human chorionic gonadotropin concentration and enrolment despite the presence of leucopenia ($<3{\cdot}0 \times 10^3/\mu L$). Another concern was our inclusion of patients with a positive Xpert MTB/RIF assay but negative sputum culture at baseline for analysis of the primary outcome. In fact, our trial involved patients with pulmonary tuberculosis with a positive Xpert MTB/RIF assay regardless of the culture status at baseline. We assumed a 10% culture failure rate in our calculation of the sample size, but

the failure rate turned out to be higher than 10%. A third concern was that the results based on the per-protocol analysis were overemphasised in the conclusion. We respectfully disagree with this comment. We suggested, rather than concluded, that linezolid might have a role in treating drug-susceptible tuberculosis based on the per-protocol analysis.

According to another suggestion, we did an additional subgroup analysis of patients with tuberculosis who showed cavitation on chest x-ray. However, no difference was found in culture conversion at 2 months or in the times to culture conversion in these patients in the modified intention-to-treat analysis. Negative cultures in liquid media at 8 weeks of treatment were observed in 39 (71%) of 55 patients in the control group, 35 (73%; p=0·82) of 48 patients in the linezolid 2 weeks group, and 41 (76%; p=0·55) of 54 patients in the linezolid 4 weeks groups. The median time to culture conversion from randomisation in liquid media was 56 days (IQR 32–58) in the control group, 32 days (28–54; p=0·06) in the linezolid 2 weeks group, and 30 days (14–56; p=0·12) in the linezolid 4 weeks group.

Finally, a concern was raised regarding the use of linezolid, a potentially toxic drug, for pulmonary tuberculosis without any resistance. We believe that any physician who has seen the substantial effects of linezolid for patients with multidrug-resistant tuberculosis[4] wonders whether this drug can be safely used to improve the treatment outcome in patients with drug-susceptible pulmonary tuberculosis. The results of our trial[3] show that use of linezolid for up to 4 weeks is safe and potentially effective for pulmonary tuberculosis without the development of resistance.

We declare no competing interests.

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1 Bilgin H, Tükenmez-Tigen E. Linezolid for drug-susceptible tuberculosis. *Lancet Infect Dis* 2019; **19:** 357–58.
2 Ahmed S, Moore DAJ, Nimmo C, Nunn AJ, Yates TA, on behalf of the North London TB Journal Club. Linezolid for drug-susceptible tuberculosis. *Lancet Infect Dis* 2019; **19:** 357–58.
3 Lee J-K, Lee JY, Kim DK, et al. Substitution of ethambutol with linezolid during the intensive phase of treatment of pulmonary tuberculosis: a prospective, multicentre, randomised, open-label, phase 2 trial. *Lancet Infect Dis* 2019; **19:** 46–55.
4 Lee M, Lee J, Carroll MW, et al. Linezolid for treatment of chronic extensively drug-resistant tuberculosis. *N Engl J Med* 2012; **367:** 1508–18.

Zika's passage to India

Kriangsak Ruchusatsawat and colleagues[1] reported an observational study of individuals with suspected Zika virus infection in Thailand between January, 2016, and December, 2017. Phylogenetic analysis suggested persistent circulation of Zika virus in Thailand since at least 2002. This finding is important because it suggests that Zika virus has the potential for endemic transmission. Although comparable data for other Asian countries are not available, concern exists about possible epidemic transmission elsewhere in Asia, particularly in India.[2] Four Zika cases were reported in India in 2016–17, which were probably due to local transmission because the individuals did not report any travel history in the past several months.[3] But travellers are also a potential source of Zika virus in India, particularly individuals from Malaysia and Singapore, where Zika cases have been reported in the past 3 years.[4]

The more recent outbreaks of Zika virus in India are a major cause for concern. In late 2018, 159 cases of Zika virus infection were reported in Rajasthan[5] and 127 in Madhya Pradesh.[6] Since most Zika virus infections are mild or asymptomatic, the extent of these outbreaks is probably underestimated, and the consequences could be severe if the pattern continues into 2019. As many as 465·7 million people in India could become infected if a major Zika virus outbreak was to occur.[7] On Dec 13, 2018, the US Centre for Disease Control and Prevention issued a level 2 alert for travellers to India, recommending enhanced precautions against Zika virus infection and advising pregnant women not to travel to affected areas.

Numerous parallels exist between India, Thailand, and the most affected countries in South America, particularly the similar climates, distribution of mosquito species, and prevalence of other arboviruses such as chikungunya and dengue. The widespread poverty and large population in India make uncontrolled spread of Zika virus likely.[8] Ruchusatsawat and colleagues[1] suggested that Zika virus in Thailand has found a so-called middle ground, with transmission levels high enough to maintain the virus but not high enough for widespread immunity to develop; perhaps a similar dynamic has been established in India.

130 pregnant women in Thailand had Zika virus infection between January, 2016, and August, 2018, of whom 119 gave birth, with four babies having microcephaly.[1,9] During this period, 285 cases of microcephaly were reported in Thailand with no maternal history of Zika virus infection. Three of these cases were identified as congenital Zika virus syndrome. No similar data exist for India, but mechanisms need to be put in place to identify Zika congenital syndrome or other serious disease manifestations in the country. We note with some concern the advisory note of the Indian Ministry of Health and Family Welfare titled *Zika virus strain that causes microcephaly not found in Rajasthan*, the content and title of which seem to imply the Zika

For the **advisory note from the Government of India** see http://pib.nic.in/newsite/PrintRelease.aspx?relid=184586